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PATENT APPLICATION
Attorney's Docket No.: 2825.1016-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jian-Bing Fan, Joel N. Hirschhorn, Xiaohua Huang, Paul Kaplan, Eric S. Lander, David J. Lockhart, Thomas Ryder, and Pamela Sklar		
Application No.:	09/536,841	Group Art Unit:	1655
Filed:	March 27, 2000	Examiner:	Wilder, C.
Title:	UNIVERSAL ARRAYS		

CERTIFICATE OF MAILING

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AMENDMENT A

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Amendment is being filed in response to the Office Action mailed from the U.S. Patent and Trademark Office on March 22, 2001 in the above-identified application. Reconsideration and further examination are requested.

An extension of time to respond to the Office Action is respectfully requested. A Petition for Extension of Time and the appropriate fee are being filed concurrently with this Amendment.

Please amend the application as follows:

In the Claims

Please cancel Claim 1.

Please amend Claims 2, 20, 21, and 22. Amendments to the claims are indicated in the attached "Marked Up Version of Amendments" (pages i - ii).

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2. (Amended) A kit comprising:

(a) an array comprising one or more oligonucleotide tags fixed to a solid substrate, wherein each oligonucleotide tag comprises a unique known arbitrary nucleotide sequence of sufficient length to hybridize to a locus-specific tagged oligonucleotide; and

(b) one or more locus-specific tagged oligonucleotides, wherein each locus-specific tagged oligonucleotide has at its first (5') end nucleotide sequence which hybridizes to the arbitrary sequence of a corresponding oligonucleotide tag on the array, and has at it's second (3') end nucleotide sequence complementary to target polynucleotide sequence in a sample wherein the last nucleotide at the 3' end of the locus-specific tagged oligonucleotide hybridizes exactly one nucleotide before the nucleotide to be queried in the target polynucleotide sequence.

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20. (Amended) A set of primers for use in determining a ratio of nucleotides present at a polymorphic locus, comprising:

(a) a pair of primers which when in the presence of a DNA polymerase amplify a region of double stranded DNA, wherein the region comprises a polymorphic locus; and

(b) an extension primer which comprises a 3' portion which is complementary to a portion of the region of double stranded DNA and a 5' oligonucleotide portion which is not complementary to the region of double stranded DNA, but which is

complementary to a unique known sequence of an oligonucleotide tag fixed to a solid substrate, wherein the extension primer is complementary to the 3' nucleotide sequence of the polymorphic locus, and wherein the last nucleotide at the 3' end of the extension primer hybridizes exactly one nucleotide before the polymorphic locus.

21. (Amended) A kit comprising in a single container two or more of the sets of primers of claim 20, and at least two labeled dideoxynucleotides, each of which is distinctly labeled.

22. (Amended) A kit comprising in a single container:

(a) a set of primers and dideoxynucleotides of claim 20; and

(b) a solid support comprising a probe which is attached to a solid support, wherein the probe is complementary to the 5' portion of the extension primer.

A2 cancelled

REMARKS

Claim Amendments

Claim 1 has been canceled.

Claim 2 has been amended to delete the superfluous phrase "e.g., is complementary to".

Claim 20 has been amended to further clarify the claim language to more precisely define the properties of the extension primer. Support for this amendment can be found in the Specification, for example at page 8, lines 3-8 and Figure 3.

Claims 21 and 22 have been amended to include in the kit at least two distinctly labeled dideoxynucleotides. Support for this amendment can be found in the Specification, for example at page 3, lines 11-13; page 8, lines 21-27; and page 12, lines 5-6.

No new matter has been added.

Rejection of Claims 1-2, 20 and 21 Under 35 U.S.C. §112, Second Paragraph

Claims 1-2, 20 and 21 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner states that Claims 1 and 2 are indefinite with regard to the phrase "for example (e.g.)" because it is unclear whether the limitations following the phrase are part of the claimed invention.

Claim 1 has been cancelled. Claim 2 has been amended to delete the phrase "e.g., is complementary to", thereby obviating the rejection.

The Examiner also states that Claims 20 and 21 are indefinite and confusing with regard to the phrase "wherein the extension primer terminates one nucleotide 5' to the polymorphic locus".

Claim 20 has been amended to further clarify the claim language to more precisely define the properties of the extension primer; Claim 21 is dependent upon Claim 20.

Thus, the claims, as amended, even more particularly point out and distinctly claim the subject matter which Applicants regard as the invention in accordance with 35 U.S.C.§112, second paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 20 and 21 Under 35 U.S.C.§102(b)

Claims 20 and 21 are rejected as being anticipated by Eyal and Navot (CA 2, 170, 950). As discussed *supra*, Claim 20 has been amended, and Claim 21 has also been amended to recite that the kit comprises at least two labeled dideoxynucleotides, each bearing a distinct label. Support for this amendment can be found in the Specification, for example, at page 13, lines 4-6.

Eyal and Navot teach a kit containing, *inter alia*, one or more marked oligonucleotide primers, and primer extension units. (See Example 6.) The kit disclosed by Eyal and Navot does not include a pair of primers for DNA amplification. The marked oligonucleotide primers are distinct from the extension primers of the present invention because the extension primers of the present invention have a 5' oligonucleotide portion which is not complementary to the region of double stranded DNA, but which is complementary to a unique known sequence of an oligonucleotide tag. The marked oligonucleotides taught by Eyal and Navot are disclosed as

being marked with such moieties as fluorescence, chemiluminescence or radioactivity (see, for example, page 22, lines 10-12).

The Examiner has quoted Eyal and Navot as teaching "a primer set and kit comprising the primer set wherein the primer set comprise a pair of primers which when in the presence of a DNA polymerase amplify a region of DNA and an extension primer . . . ." at page 6, lines 6-11, page 25, lines 24-28, and Example 6. Applicants respectfully disagree. Page 6, lines 6-11 of Eyal and Navot teach an extension primer and an "extension moiety" which is a nucleotide or nucleotide analog. There is no teaching or suggestion of a pair of primers which when in the presence of a DNA polymerase amplify a region of double stranded DNA, wherein the region comprises a polymorphic locus. Eyal and Navot, at page 25, lines 24-28, state that when "primer-dependent *in vitro* amplification products are used as genetic material for template dependant primer extension . . .", this can result in "false positive signal if the primer extension unit is labeled . . ." (in other words, if the nucleotide or nucleotide analog is labeled). Eyal and Navot do not teach the use of primer pairs to amplify DNA, but instead point out the potential for false positive results when labeled nucleotides or nucleotide analogs are used instead of labelled extension primers when PCR amplified DNA is used as source material. Furthermore, in Example 6 of Eyal and Navot provides no teaching of a kit containing a pair of primers for PCR amplification of DNA. The kit only contains, *inter alia*, extension primer(s) and a nucleotide or nucleotide analog (the primer extension units). Applicants therefore respectfully submit that Claims 20 and 21 are not anticipated by Eyal and Navot.

Rejection of Claims 20 and 21 Under 35 U.S.C. §102(b)

The Examiner has rejected Claims 20 and 21, at point 7, under the heading of **Claim rejections-35 U.S.C.§102**; however, the text of the rejection states that the rejection is under 35 U.S.C.103(a) as being unpatentable over Soderlund *et al.* (WO91/13075), and the Examiner notes in closing that "the claimed invention of Claim 20 is anticipated by the reference of Soderlund et al." Applicants respectfully request clarification of the statutory basis for the rejection. For purposes of this response, Applicants have assumed that the rejection is made under 35 U.S.C. §102(b).

Applicants respectfully traverse the Examiner's rejection of Claims 20 and 21 as being anticipated by Soderlund *et al.* Applicants note that Claim 20 has been amended herein to distinctly point out that which is regarded as the invention as discussed *supra.* The teachings of Soderlund *et al.* do not anticipate the presently claimed invention. The extension primer of Soderlund *et al.*, referred to as the detection step primer (see page 13, line 35, to page 14, line 2), does not comprise the specific components of the present invention, namely a 3' portion which is complementary to a portion of the region of double-stranded DNA and a 5' oligonucleotide portion which is not complementary to the region of double-stranded DNA, but which is complementary to a unique known sequence of an oligonucleotide tag fixed to a solid substrate, wherein the most 3' nucleotide of the extension primer hybridizes exactly one nucleotide before the polymorphic locus. Since Soderlund *et al.* does not teach every component of Claims 20 and 21, as amended, this reference does not anticipate the present invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 22-23 Under 35 U.S.C. §102(b)

The Examiner has rejected Claims 22-23, at point 8, under the heading of **Claim rejections-35 U.S.C.§102**; however, the text of the rejection states that the rejection is under 35 U.S.C.103(a) as being unpatentable over Wallace et al., and the Examiner notes in closing that the claimed invention "is anticipated by the reference of Wallace et al." Applicants respectfully request clarification of the statutory basis for the rejection. For purposes of this response, Applicants have assumed that the rejection is made under 35 U.S.C. §102(b).

Applicants respectfully disagree with the Examiner's rejection. The Examiner has quoted Wallace *et al.* at page 5, lines 19-20, as teaching a diagnostic kit. Wallace *et al.* at page 5, lines 19-20, state that "kits for performing such diagnosis are provided.." However, the actual components of such a kit are not disclosed by Wallace *et al.* Therefore, Wallace *et al.* do not disclose a kit which contains the components recited in Claim 22 or 23, and cannot anticipate the claimed invention. Furthermore, the present invention provides for the use of at least two distinctly labeled dideoxynucleotides. Wallace *et al.* teach the use of a single labeled deoxynucleotide triphosphate in a single reaction to yield a product if, and only if, the correct deoxynucleotide triphosphate is present (see, for example, page 5, lines 5-8), and Wallace *et al.*

do not teach the use of at least two distinctly labeled dideoxynucleotides. Thus the present invention is clearly distinguishable and novel in view of Wallace *et al.* Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1 and 2 Under U.S.C.§102(a)

Claims 1 and 2 are rejected as being anticipated by Wong *et al.* (WO 98/15644). Claim 1 has been cancelled, and Claim 2 has been amended herein.

Wong *et al.* teaches the sequencing of DNA using tag primers. The tag primers of Wong *et al.* hybridize at their 3' end to a tag vector. The tag vector contains a cloning site, into which the DNA of interest to be sequenced is inserted (see, for example, page 14, lines 9-15). The 3' tag sequence of the Wong *et al.* extension primer is thus designed to hybridize to a sequence contained in the recombinant vector, into which the DNA of interest to be sequenced is also cloned at an unspecified distance from the tag sequence. In contrast, the present invention discloses locus-specific tagged oligonucleotides that hybridize directly to the double-stranded DNA of interest, exactly one nucleotide adjacent to the polymorphic nucleotide to be queried. Applicants respectfully submit that a closer review of Wong *et al.* will demonstrate that Claim 2, as amended, is not anticipated by Wong *et al.* Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 24 and 25 Under 35 U.S.C.§103(a)

Claims 24 and 25 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Wallace *et al.* in view of Wong *et al.* As discussed above, Wallace *et al.* does not provide any teaching of a diagnostic kit meeting the requirements of the claims of the present application; in fact, there is no description of the components of the kit of Wallace *et al.* Moreover, as discussed above, the oligonucleotides that are attached to the solid support of Wong *et al.* are distinct from those of the present invention. Thus, even the combination of the teachings of Wallace *et al.* with those of Wong *et al.* does not teach all of the components of the claimed invention, and therefore this combination cannot render obvious Claims 24 and 25. Reconsideration and withdrawal of the rejection are respectfully requested.

Information Disclosure Statement

A Supplemental Information Disclosure Statement (IDS) was filed on April 4, 2001. A Second Supplemental Information Disclosure Statement (IDS) is being filed concurrently herewith. Entry of the both the Supplemental and Second Supplemental IDS is respectfully requested. Applicants request that the cited references be considered and that copies of the PTO 1449 forms initialed to indicate consideration by the Examiner be returned with the next Communication.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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